

Research Design in *Ethics and Ebola: Public Health Planning and Response*

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I. Introduction

In *Ethics and Ebola: Public Health Planning and Response* (*Ethics and Ebola*), the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) emphasized a pressing need to improve key elements of the U.S. planning and response capabilities for public health emergencies.¹ The Bioethics Commission provided an overview of key ethical challenges related to the 2014-2015 Ebola epidemic and endorsed ongoing participation of the United States in the global response for both ethical and prudential reasons. The Bioethics Commission analyzed two specific issues of concern: 1) the ethical use of liberty-restricting public health measures and 2) research ethics during public health emergencies.

¹ Presidential Commission for the Study of Bioethical Issues (PCSB). (2015, February). *Ethics and Ebola: Public Health Planning and Response*. Washington, DC: PCSBI.

II. Learning Objectives

After completing this activity, students should be able to:

1. Understand key ethical challenges that arise when conducting clinical research during public health emergencies.
2. Discuss ethically relevant considerations in designing research during a public health emergency.
3. Describe the ethical considerations of various approaches to clinical research during public health emergencies, including randomized controlled trials.

III. Background

Research design encompasses the entire span of a research project, from its earliest stages, when researchers review other relevant scientific theory and research findings to formulate questions and hypotheses, to the final analyses, to reporting of results and disposition of the data.² A rigorous research design yields outcomes that have scientific validity (results are accurate and reflect reality) and reliability (results can be replicated consistently).³ A strong research design also uses appropriate methods to answer the scientific question at hand.⁴

Clinical research during a public health emergency is important, especially in cases like the 2014-2015 Ebola epidemic, for which there were no licensed and approved vaccines or curative treatments. Designing protocols for clinical trials for preventive and treatment interventions raises difficult ethical, scientific, and practical questions. The fear and desperation associated with epidemics, coupled with a heightened sense of urgency, can raise challenges for the interpretation and practical application of ethical principles for human subjects research during a public health emergency.

² Boeije, H.R. (2010). *Analysis in Qualitative Research*. Thousand Oaks, CA: SAGE Publications; Parfrey, P.S., and P. Ravani. (2015). On Framing the Research Question and Choosing the Appropriate Research Design. In P.S. Parfrey and B.J. Barrett. (Eds.). *Clinical Epidemiology: Practice and Methods*, Second Edition (pp. 3-18). New York, NY: Humana Press; USC Libraries. (2015). Organizing Your Social Sciences Research Paper: Types of Research Designs [Webpage]. Retrieved September 30, 2015 from <http://libguides.usc.edu/c.php?g=235034&p=1559832>.

³ Trochim, W.M.K. (2006). Research Methods Knowledge Base: Introduction to Validity [Webpage]. Retrieved September 30, 2015 from <http://www.socialresearchmethods.net/kb/introval.php>; Winter, G. (2000). A comparative discussion of the notion of 'validity' in qualitative and quantitative research. *The Qualitative Report*, 4(3&4). Retrieved September 30, 2015 from <http://www.nova.edu/ssss/QR/QR4-3/winter.html>.

⁴ See the *Research Design Background* for more information about ethical research designs. The module is available at <http://www.bioethics.gov/education>.

A. Randomized Controlled Trials

Randomized controlled trials are considered the ideal scientific standard for determining the safety and efficacy of a treatment or vaccine. Well-designed and implemented randomized controlled trials yield credible results, greater ease in determining the safety and efficacy of a new intervention, and increased likelihood of interpretable findings. Trial designs without a control group are vulnerable to errors that could make determining the safety, efficacy, and effectiveness of a new intervention difficult; could complicate the task of yielding interpretable results; and could lack validity.⁵

In the context of an Ebola outbreak, randomized controlled trials can offer the most reliable and efficient way to identify potential benefits or harms of experimental interventions, especially because there are few existing data on the safety and efficacy of the experimental interventions and currently no approved drugs or vaccines for Ebola.⁶ Despite the urgency of a public health emergency, taking all measures possible to increase the likelihood that research results will yield a credible determination about the safety, efficacy, and effectiveness of a novel intervention is imperative.⁷ Properly designed randomized controlled trials are generally best at meeting these needs; however when not feasible, other trial designs should be considered as a means to address these goals.

Some scholars argue that, in a public health emergency like the 2014-2015 Ebola epidemic—with a high mortality rate—all participants in a clinical trial should receive at least the possibility of benefit from experimental interventions.⁸ Those who argue against trials with control arms support alternative research designs that could provide access to experimental interventions to as

⁵ Confounding occurs when a third factor that is correlated with both the explanatory and response variable influences the observed effect of the variable under investigation, but is not causally in between the explanatory variable and the response variable. Effect modification occurs when the magnitude of the observed effect of the variable under investigation differs depending on a third factor. Greenland, S., and H. Morgenstern. (1989). Ecological bias, confounding, and effect modification. *International Journal of Epidemiology*, 18(1), 269-274; U.S. Food and Drug Administration (FDA). (2010, February). Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics (Draft Guidance). Retrieved June 29, 2015 from <http://www.fda.gov/downloads/Drugs/Guidances/ucm201790.pdf>; Cox, E., Borio, L., and R. Temple. (2014). Evaluating Ebola therapies—the case for RCTs. *New England Journal of Medicine*, 371(25), 2350-2351; Borio, L., Assistant Commissioner for Counterterrorism Policy; Director, Office of Counterterrorism and Emerging Threats, U.S. Food and Drug Administration (FDA). (2015). Ethical Issues Associated with Research in the Context of a Public Health Emergency. Presentation to the Bioethics Commission, February 5. Retrieved June 29, 2015 from <http://bioethics.gov/node/4590>.

⁶ Cox, E., Borio, L., and R. Temple. (2014). Evaluating Ebola therapies—the case for RCTs. *New England Journal of Medicine*, 371(25), 2350-2351.

⁷ Presidential Commission for the Study of Bioethical Issues (PCSB). (2011, December). *Moral Science: Protecting Participants in Human Subjects Research*. Washington, DC: PCSBI, p. 90.

⁸ Adebamowo, C.A., et al. (2014). Randomised controlled trials for Ebola: Practical and ethical issues. *Lancet*, 384(9952), 1423-1424.

many individuals as possible, while also generating scientifically adequate data about their safety and effectiveness.⁹

RANDOMIZED CONTROLLED TRIALS

Randomized controlled trials are widely considered to provide the most credible scientific evidence of the safety and efficacy of preventive or therapeutic clinical or public health interventions, although they are not always optimal, feasible, or ethical in every context, and the results can be difficult to extrapolate to nonresearch contexts. The design of randomized controlled trials involves assigning research participants, by chance (randomly), to one of two or more groups, each receiving a different “intervention condition,” such as an experimental drug or no experimental drug or placebo (an inactive substance used for comparison that appears as much as possible identical to the experimental intervention) and a set of standard health services. At the end of the study, data from each group are analyzed and compared to answer questions set at the outset of the trial—for example, whether the drug is safe or works to alleviate the symptoms of or cure a particular illness.

Source: Presidential Commission for the Study of Bioethical Issues (PCSB). (2015, February). *Ethics and Ebola: Public Health Planning and Response*. Washington, DC: PCSBI, p. 32.

Clinical research during a public health emergency creates a stark ethical dilemma: On the one hand, using placebo controls appears to deny some patients the possibility of benefit from experimental interventions, however small and uncertain; on the other hand, research that does not yield conclusive results about an intervention’s safety or effectiveness could exacerbate the tragedy of the epidemic by providing misleading and potentially harmful information.

B. Relevant Considerations

In *Ethics and Ebola*, the Bioethics Commission discussed four considerations that can help to address the tension between choosing a research design that prioritizes efficiency and clarity in results and another design that might offer a chance of benefit to more participants but could take longer, require more participants, or complicate the task of yielding interpretable results. The Bioethics Commission considered (1) the differences between vaccine and treatment trials, (2) the interpretation of “best available” supportive care, (3) the necessity of the research to be responsive to the host community, and (4) the importance of designing a trial that can yield scientifically valid results.

⁹ Edwards, S.J. (2013). Ethics of clinical science in a public health emergency: Drug discovery at the bedside. *American Journal of Bioethics*, 13(9), 3-14.

Vaccine and treatment trials are different in ethically relevant ways. Participants in treatment trials typically have been diagnosed with the disease and could potentially benefit from an experimental intervention. However, participants in vaccine trials are usually healthy and therefore do not have an opportunity to benefit in the same way from participating in the trial.¹⁰ Without the prospect of direct benefit, research risks must be evaluated differently.

Proponents of randomized controlled trials for experimental Ebola treatments argue that those in the control group should receive the best available supportive care. The Bioethics Commission identified two important ethical considerations regarding supportive care. First, the determination of what constitutes best available is complex. Best available supportive care might be interpreted as best *possible* supportive care, requiring the most sophisticated interventions regardless of local availability or expense. Alternatively, it might be interpreted as the *local de facto* standard of care that is available where the trial takes place and is available to all patients, regardless of whether they participate in a research trial. This level of care might be low depending on the resources available in the setting. The Bioethics Commission supported the position that the most appropriate comparator for an experimental treatment in a research trial during an emergency is the best supportive care that is available and sustainable in the community in which the research is conducted and where the intervention will be used. In addition, the Bioethics Commission recognized that determining the effectiveness of different levels of supportive care is itself an important topic for further clinical research.¹¹

The Bioethics Commission emphasized that it is ethically important for clinical research to be responsive to the health needs of the community in which the research is conducted. Community-level concerns related to the design of clinical research, including mistrust of health care workers, reluctance to seek medical care, or social unrest, should be addressed through community engagement.

Finally, the Bioethics Commission recognized that—similar to other types of scientific research—clinical research must be designed such that it can yield scientifically valid results that

“So this is again a classical ethical tension that...thoughtful people have written about literally for decades. It's the age-old tension of a randomized trial where on the one hand, it is in our ethical and human best interest to have an efficient and valid [treatment] trial where we learn as quickly as possible with methods we can rely on whether the experimental intervention works or not, and this equally profoundly important need for us always to [recognize] that there are human beings behind [this research] who are sick and desperately want and deserve whatever we know to be helpful and people who understandably want access....”

Kass, N., Phoebe R. Berman Professor of Bioethics and Public Health, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health; Director for Public Health, Berman Institute of Bioethics. (2015). Ethical Issues Associated with Research in the Context of a Public Health Emergency. Presentation to the Bioethics Commission, February 5. Retrieved February 18, 2015 from <http://bioethics.gov/node/4590>.

¹⁰ Jonsen, A.R., and F.G. Miller. (2008). Research with healthy volunteers. In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics* (pp. 481-487). New York, NY: Oxford University Press.

¹¹ Presidential Commission for the Study of Bioethical Issues (PCSB). (2015, February). *Ethics and Ebola: Public Health Planning and Response*. Washington, DC: PCSBI, pp. 38-39.

are amenable to definitive scientific interpretation; otherwise, the risks to the research participants cannot be justified.

With these considerations, the Bioethics Commission underscored the importance of selecting a trial design that can answer the research question and is ethically and practically acceptable to the community in which the research will be conducted. These ethical constraints on clinical research are important to ensuring that—in an emergency context when conducting research might seem to be secondary to the more urgent tasks of containing the crisis—the basic interests of research participants are protected and, as far as possible, advanced.¹²

Ethical public health emergency response should also consider the different ethical aspects of short- and long-term goals. In the short term, patient access to evidence-based supportive care and stable health care infrastructure is imperative. In the midst of an epidemic, providing access to experimental interventions might be less ethically important than ensuring that those participating in research and their communities benefit from what we already know about how to control and treat the disease through supportive care. For the long-term benefit of communities likely to be affected by public health emergencies in the future, reliable and accurate scientific data about the effectiveness of vaccines and treatments is critical; alongside other principal areas of research, such as factors associated with survival, disease natural history, the most effective way to deliver care from a cultural perspective, and the long-term impact of the disease on survivors and communities. In the case of Ebola, without such evidence, these and other communities might be deprived of lifesaving interventions in the next Ebola epidemic, or be economically harmed by using scarce health care resources for interventions that are ineffective against the disease.

C. Bioethics Commission Recommendations

The Bioethics Commission made seven recommendations in *Ethics and Ebola*, one of which pertains directly to research design. With regard to the Ebola epidemic, the Bioethics Commission's sixth recommendation stressed that clinical research should include the best supportive care that is available and sustainable in the community in which research is conducted, and that clinical trials should be methodologically rigorous and capable of generating results that are clearly interpretable, acceptable to the host communities, and minimize delays to completing the research.

Recommendation 6:

Research during the Ebola epidemic should provide all participants with the best supportive care sustainably available in the community in which the

¹² London, A.J. (2016). Research in a Public Health Crisis: The Integrative Approach to Managing the Moral Tensions. In B. Jennings, et al. (Eds.). *Emergency Ethics: Public Health Preparedness and Response*. New York, NY: Oxford University Press.

research is conducted. Trial designs should be methodologically rigorous and capable of generating results that are clearly interpretable, acceptable to the host communities and, to the extent possible, minimize delays to completing the research. Properly designed placebo-controlled trials can meet these conditions, and innovative designs, such as adaptive randomization, ought to be considered as a means of addressing these research goals. Research teams should actively engage with affected communities while planning research to determine the trial design that best reflects these ethical and scientific requirements.

IV. Reading

For the purposes of discussion, students should download and read the following Bioethics Commission materials (reports are available for download on the Bioethics Commission's website at www.bioethics.gov under "Projects"):

Ethics and Ebola: Public Health Planning and Response, pp. 32-51 ("Research Ethics during Public Health Emergencies").

V. Discussion Questions

The following questions are based on the information provided above and through the indicated reading and are intended to reinforce important aspects of ethical research design during public health emergencies that are highlighted in *Ethics and Ebola*. Important points are noted with each question to help the instructor guide group discussion. The "Additional Resources" section is a helpful source in answering these questions.

1. What are the arguments for and against the use of randomized controlled clinical trials during a public health emergency?

Starting points for discussion:

- a. The argument for randomized controlled clinical trials
 - i. Random assignment of participants into treatment and control groups is widely considered the ideal standard for avoiding biases or incomplete conclusions.
 - ii. One proposed alternative to randomizing participants into treatment and control groups is to compare those taking an experimental intervention with historical control subjects. However, validity could be threatened if the

historical control subjects differ in relevant ways from those in the clinical trial.

- iii. Data that lack validity and reliability can jeopardize the interpretation of results. Despite the urgency of a public health emergency, a credible determination about the safety, efficacy, and effectiveness of an experimental intervention is critical. Mistakenly attributing a benefit or missing a potential harm can directly harm study participants and future recipients of the intervention, if it is implemented.
- b. The argument against randomized controlled clinical trials
- i. In situations where the risk of fatality or other harm from the underlying disease is substantial, randomization could deny participants “at least the possibility of benefit” that they might receive from an experimental intervention.¹³
 - ii. Alternative trial designs can provide access to experimental interventions to more many individuals while still generating scientifically adequate data. A potential benefit of alternative designs, if they are feasible, is that availability of an experimental drug might encourage affected individuals to go to treatment centers earlier, thus potentially ameliorating their suffering and helping to contain an epidemic.

2. In an emergency, what are ethically relevant considerations when choosing between a research design that prioritizes efficiency and clarity of results and an alternative design that might offer the chance of potential benefit to more participants?

Starting points for discussion:

- a. When considering the use of a randomized controlled trial, it is important to note that the ethical challenges raised in the context of vaccine trials can be different from those raised by treatment trials. Whereas the participants of a treatment trial typically have been diagnosed with a particular disease and might benefit from participation, the participants of a vaccine trial are healthy volunteers.¹⁴ They therefore do not stand to benefit from the trial in the same way that a treatment-trial participant might. However, some participants at higher risk for contracting the disease, such as health

¹³ Adebamowo, C.A., et al. (2014). Randomised controlled trials for Ebola: Practical and ethical issues. *Lancet*, 384(9952), 1423-1424.

¹⁴ Jonsen, A.R., and F.G. Miller. (2008). Research with healthy volunteers. In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics* (pp. 481-487). New York, NY: Oxford University Press.

- care workers, might receive an individual benefit if the vaccine being studied proves effective.
- b. The context in which an epidemic occurs can add important ethical complexities. In an epidemic that occurs in a resource-poor setting, as was the case in the 2014-2015 Ebola epidemic, it is critical to distinguish between the best possible supportive care which might not be readily available and the local *de facto* supportive care which might be very minimal.
 - c. Decisions about research design also should ensure that research is responsive to the needs of the community in which the research is conducted. In addition, researchers should consider whether randomized controlled trials could cause or exacerbate mistrust of health care workers, and if so, consider alternative trial designs.
 - d. All clinical research must be designed such that it can yield scientifically valid results that are amenable to definitive scientific interpretation; otherwise, the risks to the research participants cannot be justified.

VI. Problem-Based Learning

Scenario A: *Cholera is an intestinal infection that most often occurs in conditions of poverty or poor sanitation. Although the standard treatment for cholera involves rehydration and antibiotics, researchers over the last few decades have sought innovative ways to complement these therapies. One such intervention, a drug called racecadotril, works by preventing water secretion thereby reducing the need for intravenous fluids and the severity of the disease. In 2003, researchers in Bangladesh conducted a randomized controlled clinical trial on infected adults to evaluate the safety and efficacy of this intervention.*¹⁵

The following additional reading might be useful in considering this scenario:

Alam N.H., et al. (2003). Efficacy and tolerability of racecadotril in the treatment of cholera in adults: A double blind, randomised, controlled clinical trial. *Gut*, 52(10), 1419-1423. Retrieved September 30, 2015 from <http://gut.bmj.com/content/52/10/1419.long>.

1. What are the characteristics of cholera that make lessons from the recent Ebola epidemic relevant?

Starting points for discussion:

¹⁵ Alam N.H., et al. (2003). Efficacy and tolerability of racecadotril in the treatment of cholera in adults: a double blind, randomised, controlled clinical trial. *Gut*, 52(10), 1419-1423.

- a. Cholera outbreaks often are public health emergencies. Without treatment, the disease can be fatal.
- b. Cholera outbreaks tend to occur in settings characterized by poverty and poor sanitation. These conditions to the ethical challenges involved with ensuring equitable access to the potential benefits of the results of scientific inquiry, determining appropriate levels of supportive care in clinical trials, and exploring alternative trial designs.

2. What are some of the ethical and practical considerations about research design that researchers might encounter while studying cholera in a resource-poor setting?

Starting points for discussion:

- a. Researchers have a responsibility to consider which research methods will yield the most scientifically valid and reliable results.
- b. Engaging members of the communities—such as health care workers, patients, and community leaders, among others—in which the research will be conducted ethically enhances the research and makes the findings more relevant to affected communities. Research should be responsive to the needs of those who are affected most by the disease.
- c. The fear and desperation associated with epidemics, coupled with a heightened sense of urgency, can raise challenges for interpretation and practical application of ethical principles for human subjects research during a public health emergency.

3. Why might some individuals object to conducting a randomized controlled clinical trial with cholera patients during a public health emergency?

Starting points for discussion:

- a. In the context of an outbreak of a disease with serious health consequences or high case fatality, randomized controlled clinical trials might deny participants in the control group the possibility of benefit.
- b. Alternative trial designs might yield scientifically valid results and offer the experimental intervention to as many individuals as possible.

VII. Exercises

Exercise A: *In a phase III vaccine trial, an experimental vaccine is given to a large group of participants to test effectiveness and monitor side effects (following earlier phase studies to determine safety and efficacy). A phase III randomized controlled trial of the rVSV-ZEBOV vaccine for Ebola is underway in an Ebola-affected country. When the trial begins, there are many new cases diagnosed each week in the region. However, within a few months of the start of the trial, numbers of new cases per week decrease substantially such that enrolling the estimated number of participants is no longer possible.*

The following references provide useful information:

World Health Organization (WHO). (2015, May 26). Ebola vaccines, therapies, and diagnostics. Retrieved September 30, 2015 from http://www.who.int/medicines/emp_ebola_q_as/en/.

Centers for Disease Control and Prevention (CDC). (2015). Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE) Q&A. Retrieved September 30, 2015 from <http://www.cdc.gov/vhf/ebola/strive/qa.html>.

National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH). (2015, February 2). Ebola Vaccine Trial Opens in Liberia. Retrieved September 30, 2015 from <http://www.niaid.nih.gov/news/newsreleases/2015/Pages/PREVAIL.aspx>.

National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH). (2015, February 2). Questions and Answers: PREVAIL Phase 2/3 Clinical Trial of Investigational Ebola Vaccines. Retrieved September 30, 2015 from <http://www.niaid.nih.gov/news/QA/Pages/EbolaVaxresultsQA.aspx>.

1. **What concerns might researchers have about trial design once the number of Ebola cases decreases?**
2. **What considerations should guide researchers in deciding how to respond ethically to the change in the epidemic?**
3. **How might researchers alter the design of the trial to accommodate this change?**

VIII. Glossary of Terms

Community engagement: A mechanism to involve members of the community in the planning and execution of research, inclusive of those who will be affected by or who are in a position to influence the course of research.

Informed consent: The process of informing and obtaining permission from an individual before conducting medical or research procedures or tests.

Protocol: A plan for the conduct of a research project, including all aspects of the project from recruitment to obtaining informed consent to dissemination of results.

Vulnerable populations: Groups of individuals who are potentially unable to exercise control over how their interests are represented and pursued.

IX. Additional Resources

Adebamowo, C.A., et al. (2014). Randomised controlled trials for Ebola: Practical and ethical issues. *Lancet*, 384(9952), 1423-1424.

Committee on Science, Engineering, and Public Policy; Institute of Medicine; Policy and Global Affairs; National Academy of Sciences, National Academy of Engineering. (2009). *On Being a Scientist: A Guide to Responsible Conduct in Research*, Third Edition. Washington, DC: The National Academies Press. Retrieved September 30, 2015 from http://www.nap.edu/openbook.php?record_id=12192.

Cox, E., Borio, L., and R. Temple. (2014). Evaluating Ebola therapies—the case for RCTs. *New England Journal of Medicine*, 371(25), 2350-2351.

Edwards, S.J. (2013). Ethics of clinical science in a public health emergency: Drug discovery at the bedside. *American Journal of Bioethics*, 13(9), 3-14.

Emanuel, E.J., Wendler, D., and C. Grady. (2000). What makes clinical research ethical? *JAMA*, 283(20), 2701-2711.

Protection of Human Subjects, HHS. 45 C.F.R. Part 46.

Protection of Human Subjects, FDA. 50 C.F.R. Part 21.

World Medical Association (WMA). (2013). WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Retrieved September 30, 2015 from <http://www.wma.net/en/30publications/10policies/b3/index.html>.